REQUIREMENTS FOR REPORTING RESEARCH EVENTS TO FACILITY OVERSIGHT COMMITTEES AND THE OFFICE OF RESEARCH OVERSIGHT

1. PURPOSE. This Veterans Health Administration (VHA) Handbook sets forth the requirements for reporting certain research events to local oversight committees and to the Office of Research Oversight (ORO)(10R). ***NOTE:*** *This Handbook does not preempt or otherwise alter any other applicable research reporting requirements, whether within the Department of Veterans Affairs (VA) or to other Federal or state agencies or commercial sponsors.*

2. SUMMARY OF MAJOR CHANGES. This revised VHA Handbook:

a. Broadens the previous version of the Handbook to specify requirements for reporting certain research events to facility research oversight committees and to ORO.

b. Supersedes all previous ORO memoranda on reporting of such research events.

c. This Handbook assigns responsibilities related to reporting research events to ORO, the Directors of VA research facilities, the facility research service, facility research oversight committees, facility Research Compliance Officers (RCOs), and research investigators.

3. RELATED ISSUES. VA Directive 6502, VA Handbook 6500, VHA Directive 1058, VHA Handbook 1058.2, VHA Handbook 1058.03, VHA Handbook 1058.04, VHA Handbook 1058.05, VHA Handbook 1200.1, VHA Handbook 1200.5, VHA Handbook 1200.06, VHA Handbook 1200.7, VHA Handbook 1200.8, and VHA Handbook 1605.1.

4. RESPONSIBLE OFFICE. ORO (10R) is responsible for the contents of this Handbook. Questions may be referred to (202) 266-4577.

5. RESCISSIONS. VHA Handbook 1058.1, Reporting Adverse Events in Research to the Office of Research Oversight, dated November 19, 2004, is rescinded.

6. RECERTIFICATION. This VHA Handbook is scheduled for recertification on or before the last working day of February 2014.

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DISTRIBUTION: CO: E-mailed 3/3/2009
FLD: VISN, MA, DO, OC, OCRO, and 200 – E-mail 3/3/2009

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REQUIREMENTS FOR REPORTING RESEARCH EVENTS TO FACILITY OVERSIGHT COMMITTEES AND THE OFFICE OF RESEARCH OVERSIGHT

1. PURPOSE

This Veterans Health Administration (VHA) Handbook sets forth the requirements for reporting certain research events to facility research oversight committees and to the Office of Research Oversight (ORO)(10R). ***NOTE:*** *This Handbook does not preempt or otherwise alter any other applicable research reporting requirements, whether within the Department of Veterans Affairs (VA) or to other Federal or state agencies or commercial sponsors.*

2. BACKGROUND

ORO serves as the primary VHA office for advising the Under Secretary for Health and exercising oversight concerning all matters of research compliance and assurance, including human subject protections, laboratory animal welfare, research safety, research laboratory security, research information security, research misconduct, debarment for research impropriety, and other matters that the Under Secretary for Health may assign. ORO is responsible for developing and conducting research compliance officer education programs as directed by the Under Secretary for Health.

3. SCOPE

This Handbook:

a. Identifies the research events that must be reported to facility research oversight committees,

b. Identifies the research events that must be reported to ORO Regional Offices (ROs),

c. Identifies the research events that must be reported to ORO Central Office,

d. Provides the methods and timelines for reporting such events, and

e. Indicates what information must be provided in reports of these events.

4. DEFINITIONS

The following definitions are intended for use only within this Handbook.

a. **Administrative Hold.** An administrative hold is a voluntary interruption of research enrollments and/or ongoing research activities by an appropriate facility official, research investigator, or sponsor (including the VHA Office of Research and Development (ORD) when ORD is the sponsor). For the purposes of this Handbook:

(1) The term “administrative hold” does not apply to interruptions of research related to concerns regarding:

(a) The safety, rights, or welfare of human research subjects, research investigators, research staff, or others; or

(b) The safety or welfare of laboratory animals.

(2) The terms "suspension" and "termination" apply to research interruptions related to concerns about safety, rights, or welfare as described at preceding subparagraphs 4a(1)(a) and 4a(1)(b) (see subpar. 4v).

b. **Adverse Event (AE).** An AE is any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event, including an abnormal laboratory finding, symptom, or disease associated with the research or the use of a medical investigational test article. An AE does not necessarily have to have a causal relationship with the research, or any risk associated with the research or the research intervention, or assessment (see subpar. 4u). A local AE is one occurring at a site for which the VA investigator's Institutional Review Board (IRB) of Record is responsible. ***NOTE:*** *AEs are further discussed in VHA Handbook 1200.5.*

c. **Animal (Laboratory Animal).** An laboratory animal is a live (non-human) vertebrate used or intended for use in research, research training, experimentation, or biological testing, or for a related purpose. ***NOTE:*** *The term "animal" is further defined in VHA Handbook 1200.7.*

d. **Assurance (Assurance of Compliance).** An Assurance of Compliance is a written commitment to a Federal department or agency to ensure compliance with applicable requirements. For example, the participation of human subjects in VA research requires a Federalwide Assurance (FWA) for the Protection of Human Subjects, and the participation of laboratory animals in VA research requires a Public Health Service (PHS) Animal Welfare Assurance.

e. **Continuing Noncompliance.** Continuing noncompliance is persistent or repeated failure, either in the past or extending into the present, to satisfy VA or other Federal research requirements (see subpar. 4t).

f. **Human Research.** Human research is any research involving any of the following:

(1) One or more human subject(s).

(2) Data containing identifiable private information about one or more living individuals.

(3) One or more human biological specimen(s).

g. **Human Subject.** A human subject is a living individual about whom an investigator conducting research obtains:

(1) Data through intervention or interaction with the individual; and/or

(2) Identifiable private information. ***NOTE:*** *The term "human subject" and related terms are further defined in VA regulations and policy at Title 38 Code of Federal Regulations (CFR) Part 16 and VHA Handbook 1200.5.*

h. **Institutional Animal Care and Use Committee (IACUC).** An IACUC is a committee formally designated by an institution to ensure compliance with animal research regulations and guidelines and maintenance of an Animal Care and Use Program (ACUP). ***NOTE:*** *The term "Institutional Animal Care and Use Committee" and related terms are further defined in VHA Handbook 1200.7.*

i. **Institutional Official (IO).** The IO is the individual legally authorized as Signatory Official to commit an institution to an Assurance. The Facility Director, or equivalent, serves as IO for VA research facilities that conduct research.

j. **Institutional Review Board (IRB).** An IRB is a board, committee, or other group formally designated by an institution to review, approve, require modification in, disapprove, and conduct continuing oversight of human research. ***NOTE:*** *The term "Institutional Review Board" is further defined in VA regulations and policy at 38 CFR 16 and VHA Handbook 1200.5.*

k. **Investigator.** An investigator is any individual who conducts research, including, but not limited to: the Principal Investigator, co-investigator, local site investigator, etc. A VA investigator must uphold professional and ethical standards and practices and adhere to all applicable VA and other Federal requirements, and to the applicable VA facility's policies and procedures.

l. **Memorandum of Understanding (MOU).** An MOU is a written agreement entered into by and between two or more parties to set forth the terms, conditions, and understandings of the parties with respect to a specific activity. For example, an MOU may be developed to delineate each party's responsibilities, as allowable by law, in collaborations between two or more Federal agencies or between a Federal agency and a private entity.

m. **Principal Investigator (PI).** A PI is a qualified person designated by an applicant institution to direct a research project or program. The PI oversees scientific, technical, and the day-to-day management of the research. In the event of an investigation conducted by a team of individuals, the PI is the responsible leader of that team (see subpar. 4z).

(1) **Appointment in VA.** Any VA PI must hold a VA appointment.

(2) **Site Investigator or Site PI.** A Site Investigator or Site PI is an investigator at a site participating in a multi-site project who serves as the PI at that site.

n. **Research.** Research is a systematic investigation designed to develop or contribute to generalizable knowledge. ***NOTE:*** *The term "research" is further defined in VA regulations at 38 CFR 16 and VHA Handbook 1200.5.*

o. **Research and Development (R&D) Committee.** The R&D Committee is a committee responsible, through the Chief of Staff (COS) to the VA Facility Director, for oversight of the facility's research program and for maintenance of high standards throughout that program. ***NOTE:*** *The term "Research and Development Committee" is further defined in VHA Handbook 1200.1.*

p. **Research Compliance Officer (RCO).** The RCO is an individual whose primary responsibility is oversight of research projects. VA RCOs must conduct periodic audits of research activities in accordance with VA requirements. A VA research facility's lead RCO must report directly to the Facility Director.

q. **Research Impropriety.** For purposes of this Handbook, the term "research impropriety" refers to noncompliance with the laws, regulations, or policies regarding human subject protections, laboratory animal welfare, research safety, research laboratory security, research information security, research misconduct, and other matters as the Under Secretary for Health may assign. Research impropriety does not encompass improper procedures or conduct in areas outside of the jurisdiction of ORO, such as: waste, fraud, abuse, or fiscal mismanagement.

r. **Research Misconduct.** Research misconduct is fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results. ***NOTE:*** *The terms "fabrication," "falsification," and "plagiarism" are further defined in VHA Handbook 1058.2.*

s. **Research Oversight Committee.** For purposes of this Handbook, a Research Oversight Committee is any committee or subcommittee designated by a VA research facility to ensure compliance with Federal, VA, or facility requirements for the conduct of research (e.g., the IRB, IACUC, R&D Committee). ***NOTE:*** *The oversight committee may be operated by the facility's academic affiliate or by another VA entity, as long as the designation is defined in an MOU or other written agreement.*

t. **Serious Noncompliance.** Serious noncompliance is the failure to adhere to the laws, regulations, or policies governing VA research that:

(1) Results in substantive harm or damage (or risk of substantive harm or damage) to the safety, rights, or welfare of human subjects, research staff, or others; or

(2) Results in substantive harm or damage (or risk of substantive harm or damage) to the safety or welfare of laboratory animals; or

(3) Substantively compromises the integrity or effectiveness of research protections, either systemically or relative to a particular protocol or project.

u. **Serious AE (SAE) or Serious Problem.** For the purposes of this Handbook:

(1) An SAE in research is an AE that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth defect.

(2) A serious problem in research is one that results in:

(a) Substantive harm or damage (or risk of substantive harm or damage) to the safety, rights, or welfare of research subjects, research staff, or others; or

(b) Substantive harm or damage (or risk of substantive harm or damage) to the safety or welfare of laboratory animals.

(3) An AE or problem in research is also considered serious when medical, surgical, behavioral, social, or other intervention is needed to prevent preceding subparagraphs 4u(1) or 4u(2).

v. **Suspension or Termination of Research.** For purposes of this Handbook:

(1) Suspension refers to a temporary interruption in the enrollment of new subjects or other ongoing research activities.

(2) Termination refers to a permanent halt in the enrollment of new subjects or other research activities.

(3) The terms "suspension" and "termination" apply to interruptions related to concerns regarding:

(a) The safety, rights, or welfare of human research subjects, research investigators, research staff, or others; or

(b) The safety or welfare of laboratory animals.

(4) Suspension and termination do not include:

(a) Interruptions in human research resulting solely from the expiration of the IRB approval period.

(b) "Administrative holds" or other actions initiated voluntarily by an appropriate facility official, research investigator, or sponsor for reasons other than those described in preceding subparagraph 4v(3) (see subpar. 4a).

w. **Unanticipated or Unexpected Problem or AE.** An unanticipated or unexpected problem or AE is one that is unforeseen in terms of nature, severity, or frequency of occurrence, as documented in the protocol or other materials approved by the R&D Committee, IRB, IACUC, or other relevant oversight committee. For human research, such materials may include the informed consent document, clinical investigators' brochure, product labeling, etc.

x. **VA Facility.** A VA facility is any entity that is operated by VA, including but not limited to: VA hospitals, medical centers, and healthcare systems; space owned, leased, or rented by VA; and space that is "shared" with a non-VA entity (unless the VA space is leased to a non-VA entity and specifically designated in writing not to be used by VA or VA employees for

research). A VA facility may include multiple campuses and satellite components. The terms "facility," "VA facility," and "VA institution" are considered synonymous for purposes of this Handbook.

y. **VA Facility Director.** A VA Facility Director is the Director of a VA Medical Center or a VA Healthcare System. For the purposes of this Handbook, the terms "Facility Director" and "Medical Center Director" are considered synonymous. The Facility Director serves as the IO for VA research facilities and programs.

z. VA Investigator. A VA investigator is any individual who conducts research while acting under a VA appointment, including full and part-time employees, without compensation (WOC) employees, and individuals appointed or detailed to VA under the Intergovernmental Personnel Act (IPA) of 1970 (see 5 CFR Part 334). A VA investigator must comply with all applicable VA and VHA regulations and policies (see subpars. 4k and 4m).

aa. **VA Research.** VA research is research conducted by a VA investigator on VA time or using VA resources (regardless of location), or by a VA investigator in a VA facility as defined in subparagraph 4x. The research may be funded by VA, by other sources, or be unfunded (see subpars. 4k, 4m, and 4z). ***NOTE:*** *The term "VA Research" is further discussed in VHA Handbook 1200.1*.

5. GENERAL REQUIREMENTS FOR REPORTING RESEARCH EVENTS TO ORO

a. **Applicability.** The reporting requirements of this Handbook apply only to VA research. Appendix A summarizes the research events that must be reported to ORO.

b. **Facility Director Responsibilities.** The Facility Director is responsible for:

(1) Ensuring standard operating procedures (SOPs) are developed, written, and published providing detailed procedures to ensure the reporting requirements of this Handbook are met.

(2) Ensuring all other relevant reporting requirements both within VA and to external agencies and accrediting organizations are satisfied.

(3) Notifying ORO in writing as soon as possible but no later than 5 business days after being informed of a research event under the requirements of this Handbook. This notification is to be sent to ORO Central Office or the appropriate ORO RO, with a copy to the Veterans Integrated Service Network (VISN) Director.

(a) Although facility representatives are encouraged to contact ORO as soon as a reportable research event is suspected, the Facility Director must provide ORO with a signed, written report of each such event.

(b) A written report from the Facility Director is required whether or not disposition of the event has not been resolved at the time of the initial report.

(c) Follow-up reports detailing any additional findings and appropriate remedial actions must be provided to the appropriate ORO office at intervals and in a manner specified by that office.

(4) Developing and publishing SOPs that provide detailed procedures on how to ensure compliance in accordance with paragraphs 6, 7, 8, 9, and 10.

(5) Ensuring all other relevant requirements related to reporting research events, both within VA and to external agencies and accrediting organizations are satisfied.

c. **Contents of Reports to ORO.** Reports to ORO of research events must include:

(1) The name and any relevant Assurance number of the reporting VA facility.

(2) The title of the research project(s).

(3) The number(s) used by the facility's IRB, IACUC, or Research Service to identify the project(s).

(4) The name of any external sponsor(s) of the project(s).

(5) The funding source(s) for the project(s).

(6) A detailed description of the event being reported.

(7) A detailed description of the actions taken (or to be taken) to address the reported event, including systemic actions where warranted.

(8) The name of any agencies or organizations external to VA that were notified, or are to be notified, of the event.

6. REQUIREMENTS RELATED TO HUMAN RESEARCH

a. **Reports Within the Facility.** The facility Director is responsible for ensuring SOPs are established and published to ensure compliance with the reporting requirements in subparagraphs 6a(1) through 6a(5).

(1) **Problems Involving Risks to Subjects or Others**. Investigators, RCOs, and other members of the VA research community must report all problems involving, or suggesting, risks to subjects or others in VA research to the Associate Chief of Staff for Research (ACOS for R) and the IRB as soon as possible but no later than 5 business days after becoming aware of the problem. Such problems include, but are not limited to:

(a) Interruptions of subject enrollments or other research activities due to concerns about the safety, rights, or welfare of human research subjects, research staff, or others.

(b) Any work-related injury to personnel involved in human research, or any research-related injury to any other person, requiring more than minor medical intervention or that leads to serious complications or death.

(c) Any VA National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to one or more of the facility's research projects.

(d) Any Data Monitoring Committee (DMC) report describing a safety problem.

(e) Any sponsor analysis describing a safety problem. ***NOTE:*** *Sponsor "AE Reports" lacking meaningful analysis are not considered problems.*

(2) **SAEs.** VA investigators must report all local SAEs in VA research to the ACOS for R and the IRB as soon as possible, but no later than 5 business days after the event has become known to the investigator (see subpar. 4c).

(3) **IRB Review of SAEs and Problems Involving Risks to Subjects or Others.** Within 5 business days after a report of a problem involving risks to subjects or others or a local SAE, a qualified IRB member-reviewer (or alternatively, the convened IRB) must determine and document whether or not the problem is serious, whether or not it is anticipated or unanticipated, and whether it is related, possibly related, or probably not related to the research.

(a) The qualified IRB member-reviewer (or the convened IRB) must also document whether or not one of the following applies:

1. Immediate action (e.g., suspension of activities; notification of subjects) is necessary to prevent an immediate hazard to subjects in accordance with VA regulations at 38 CFR 16.103(b)(4)(iii), and review by the convened IRB is needed; or

2. Review by the convened IRB is needed, but immediate action to prevent an immediate hazard to subjects is not warranted.

(b) If the preceding determinations are made by a qualified IRB member-reviewer, the determinations must be reported to the IRB at the IRB's next convened meeting.

(c) If the qualified IRB member-reviewer (or the convened IRB) determines that the problem or AE is serious, unanticipated, and related, or possibly related, to the research, the IRB Chairperson must report the problem or event to the Facility Director as soon as possible, but no later than 5 business days after the determination.

(d) If it is determined that an informed consent modification is warranted, the convened IRB must determine and document in its records whether or not previously enrolled subjects must be notified of the modification and, if so, when such notification must take place and how such notification must be documented.

NOTE: *Appendix B provides information and decision charts related to reporting SAEs and problems involving risks to subjects or others, to the IRB and to ORO. SOPs must be developed providing detailed instructions on such reporting.*

(4) **Serious or Continuing Noncompliance**. Within 5 business days of becoming aware of possible serious or continuing noncompliance with VA or other Federal requirements related to human research (e.g., VHA Handbook 1200.5; the Common Rule at 36 CFR 16; Food and Drug Administration (FDA) regulations at 21 CFR 50 and 56) or with IRB requirements or determinations, members of the VA research community must report the possible noncompliance to the ACOS for R and the IRB. ***NOTE:*** *For purposes of this Handbook, "possible serious or continuing noncompliance" includes all findings of noncompliance related to human research by any VA office, any other Federal department or agency (e.g., FDA), or any other entity.*

(a) If the IRB determines that the possible noncompliance is or was serious or continuing, the IRB Chairperson must report the noncompliance to the Facility Director and the R&D Committee as soon as possible, but no later than 5 business days after the IRB's determination.

(b) In addition to the requirements in preceding subparagraphs 6a(4) and 6a(4)(a), an RCO identifying serious or continuing noncompliance, during an informed consent or regulatory audit, must report the noncompliance to the Facility Director, the ACOS for R, the R&D Committee, and the IRB as soon as possible but no later than 5 business days after becoming aware of the noncompliance.

(5) **Terminations or Suspensions of IRB Approval.** The IRB Chairperson must report terminations or suspensions of IRB approval of any research related to concerns about the safety, rights, or welfare of human research subjects, research staff, or others to the Facility Director as soon as possible, but no later than 5 business days after the IRB's action.

b. **Reports to ORO ROs.** The Facility Director must report the following research events to the appropriate ORO RO as soon as possible but no later than 5 business days after being informed of them (see App. A).

(1) **Problems in VA Research.** Any problem in VA research that is determined, according to subparagraph 6a(3), to involve serious risks to subjects or others, and be unanticipated and related, or possibly related, to the research.

(2) **AEs**. Any AE in VA research that is determined, according to subparagraph 6a(3), to be serious (i.e., an SAE) and unanticipated and related, or possibly related, to the research.

(3) **Serious or Continuing Noncompliance**. Noncompliance determined by the IRB or identified by an RCO, during an informed consent or regulatory audit, to be serious or continuing.

(a) The Facility Director must simultaneously report serious or continuing noncompliance identified by an RCO, during an informed consent or regulatory audit, to the Director of the VISN, or designee, in which the facility is located and the VHA Chief Research and Development Officer (CRADO), or designee.

(b) Reports based on findings made by entities external to the facility must include a copy of the entity's official findings.

(4) **Terminations or Suspensions of IRB Approval.** Terminations or suspensions of IRB approval of research that are related to concerns about the safety, rights, or welfare of human research subjects, research staff, or others.

c. **Reports to ORO CO.** The Facility Director must report the following research events to ORO CO, with a copy to the appropriate ORO RO, as soon as possible, but no later than 5 business days after being informed of them (see App. A, Table 2).

(1) **Assurance Changes.** Any change in the facility's FWA, or other ORO-approved Assurance.

(2) **IRB Changes.** Any change in the facility's designated IRB(s).

(3) **MOU Changes.** Any change in an MOU with an affiliate institution or other entity related to the designation of IRB(s) or other human research protection arrangements.

(4) **Accreditation Problems.** Failure of the VA facility to achieve the accreditation status required by ORD for human research protections, any change in the facility's accreditation status, or any change in the accreditation status of an affiliate involved in the facility's human research protection program.

7. REQUIREMENTS RELATED TO ANIMAL RESEARCH

a. **Reports Within the VA Facility.** The Facility Director must ensure written SOPs are established and published to effect compliance with the reporting requirements in subparagraphs 7a(1) through 7c(3).

(1) Investigators, RCOs, and other members of the VA research community must report the research events listed in subparagraphs 7b and 7c to the ACOS for R and the IACUC as soon as possible, but no later than 5 business days after becoming aware of them.

(2) An ACOS for R or an IACUC Chairperson must report the research events listed in subparagraphs 7b and 7c to the Facility Director and the R&D Committee as soon as possible, but no later than 5 business days after becoming aware of them.

(3) An RCO identifying serious or continuing noncompliance, during a regulatory audit, must report the noncompliance to the Facility Director, the ACOS for R, the R&D Committee, and the IACUC as soon as possible, but no later than 5 business days after becoming aware of them.

b. **Reports to ORO ROs.** The Facility Director must report the following research events to the appropriate ORO RO as soon as possible, but no later than 5 business days after being informed of them (see App. A, Table 1).

(1) **Unanticipated Incidents**. Any unanticipated incident that seriously affects the health or safety of laboratory animals, including any theft or escape of animals must be reported.

(2) **Unanticipated Loss of Life.** Any unanticipated loss of animal life, including loss due to physical plant deficiencies or engineering failures or mishaps must be reported. ***NOTE:*** *In large breeding colonies, occasional loss of life of an individual animal can be anticipated based on natural or otherwise anticipated mortality rates. This type of loss need not be reported.*

(3) **Work-Related and Other Injuries.** Any work-related injury to personnel involved in animal research, or any research-related injury to any other person, that requires more than minor medical intervention or leads to serious complications or death, must be reported.

(4) **Serious or Continuing Noncompliance.** Any serious or continuing noncompliance with, or deviations from, VA or other Federal requirements related to animal research (e.g., VHA Handbook 1200.7, the Animal Welfare Act at 9 CFR 1, 2, and 3; the PHS Policy on Humane Care and Use of Laboratory Animals; the Guide for the Care and Use of Laboratory Animals) must be reported. ***NOTE:*** *This includes animal research that is conducted beyond the expiration date established by the IACUC without appropriate renewal of the protocol, even if the research is a continuation of work that was previously approved.*

(5) **Suspensions or Terminations**. Suspensions or terminations of ongoing animal research activities related to concerns regarding the safety or welfare of laboratory animals or the safety, rights, or welfare of research staff or others, or due to operational problems that necessitate a voluntary or involuntary interruption in the conduct of animal research, must be reported.

(a) Such operational problems include the unanticipated resignation of an individual essential to the program (e.g., Veterinary Medical Officer or Veterinary Medical Unit Supervisor), a disease outbreak that threatens colony health, or physical plant issues that must be addressed to remain in compliance with VA or other Federal requirements must be reported.

(b) Such suspensions or terminations are to be reported whether they impact a specific study or the entire program.

(6) **External Noncompliance Findings.** Any findings of noncompliance related to animal research by any VA office, any other federal department or agency (e.g., the United States Department of Agriculture), or any other entity must be reported. The Facility Director's report to ORO must include a copy of the entity's official findings.

c. **Reports to ORO Central Office.** The Facility Director must report the following research events to ORO Central Office, with a copy to the appropriate ORO RO, as soon as possible, but no later than 5 business days after being informed of them (see App. A, Table 2).

(1) **Assurance Changes.** Any change in the facility's Animal Welfare Assurance status as filed with the PHS Office of Laboratory Animal Welfare (OLAW), or in the Animal Welfare Assurance status of an affiliate institution or other entity upon which the facility relies, must be reported.

(2) **MOU Changes.** Any change in an MOU with an affiliate institution or other entity regarding laboratory animal welfare or animal care and use arrangements, must be reported.

(3) **Accreditation Problems.** Failure of the VA facility to achieve the accreditation status required by ORD for animal care and use programs, any change in the facility's accreditation status, or any change in the accreditation status of an affiliate involved in the facility's animal care and use program, must be reported.

8. REQUIREMENTS RELATED TO RESEARCH SAFETY

a. **Reports Within the VA Facility.** The Facility Director must ensure written SOPs are established and published to effect compliance with the reporting requirements in subparagraphs 8a(1) through 8c.

(1) Investigators, RCOs, and other members of the VA research community must report the research events listed in subparagraphs 8b and 8c of this Handbook to the ACOS for R and the Subcommittee on Research Safety (SRS) as soon as possible, but no later than 5 business days after becoming aware of them.

(2) An ACOS for R or an SRS Chairperson must report the research events listed in subparagraphs 8b and 8c to the Facility Director and the R&D Committee as soon as possible, but no later than 5 business days after becoming aware of them.

(3) An RCO identifying serious or continuing noncompliance, during a regulatory audit, must report the noncompliance to the Facility Director, the ACOS for R, the R&D Committee, and the SRS as soon as possible, but no later than 5 business days after becoming aware of them.

b. **Reports to ORO ROs.** The Facility Director must report the following research events to the appropriate ORO RO as soon as possible, but no later than 5 business days after being informed of them (see App. A, Table 1).

(1) **Work-Related and Other Injuries.** Any work-related injury to personnel in VA research, or any research-related injury to any other person, that requires more than minor medical intervention or leads to serious complications or death.

(2) **Work-Related Exposures.** Any work-related exposure of VA research personnel to hazardous materials at greater than routine levels or that requires more than minor medical intervention or leads to serious complications or death.

(3) **Serious or Continuing Noncompliance.** Any serious or continuing noncompliance with VA or other Federal requirements related to research safety (e.g., VHA Handbook 1200.06; VHA Handbook 1200.8; 7 CFR 331; 9 CFR 121; 29 CFR 1910 and 1960; and 42 CFR 72 and 73).

(4) **Suspensions or Terminations**. Suspensions or terminations of ongoing research activities related to concerns regarding the safety, rights, or welfare of research staff or others (see subpar. 4v).

(5) **Laboratory Decommissions.** Laboratory space that is being reassigned, vacated, or converted to non-laboratory use and requires identification and disposal of hazardous materials and/or equipment between uses. ***NOTE:*** *Such laboratory decommissions must also be reported to the VISN Safety Office.*

(6) **External Noncompliance Findings.** Any findings of noncompliance related to research safety by any VA office, any other Federal department or agency (e.g., United States Environmental Protection Agency), or any other entity (e.g., State Environmental Protection Agency). The Facility Director's report to ORO must include a copy of the entity's official findings.

c. **Reports to ORO Central Office.** As soon as possible, but no later than 5 business days after being informed of any change in an MOU with an affiliate institution (or other entity related to research safety arrangements), the Facility Director must report the change to ORO Central Office, with a copy to the appropriate ORO RO (see App. A, Table 2).

9. REQUIREMENTS RELATED TO RESEARCH LABORATORY SECURITY

a. **Reports Within the VA Facility.** The Facility Director must ensure written SOPs are established and published to effect compliance with the reporting requirements in subparagraphs 9a(1) through 9c.

(1) Investigators, RCOs, and other members of the VA research community must report the research events listed in subparagraphs 9b and 9c of this Handbook to the ACOS for R as soon as possible, but no later than 5 business days after becoming aware of the problem.

(2) An ACOS for R must report the research events listed in subparagraphs 9b and 9c to the Facility Director and the R&D Committee as soon as possible, but no later than 5 business days after becoming aware of them.

(3) An RCO identifying serious or continuing noncompliance, during a regulatory audit, must report the noncompliance to the Facility Director, the ACOS for R, and the R&D Committee as soon as possible, but no later than 5 business days after becoming aware of them.

b. **Reports to ORO ROs.** The Facility Director must report the following research events to the appropriate ORO RO as soon as possible, but no later than 5 business days after being informed of them (see App. A, Table 1).

(1) **Injuries.** Any injury or harm to a human individual or laboratory animal related to a break-in, security breach, or other security problem involving a VA research facility.

(2) **Serious or Continuing Noncompliance.** Any serious or continuing noncompliance with Federal, VA, or VHA requirements related to research laboratory security.

(3) **Biosafety Level 3 (BSL-3) Breaches**. Any break-in or security breach involving a VA BSL-3 research laboratory.

(4) **Other Breaches.** Any break-in or security breach involving a VA research facility that results in any of following:

(a) Loss of any quantity of a select agent or toxin.

(b) Loss of any quantity of a highly hazardous agent (see VHA Handbook 1200.06).

(c) Substantial damage to the facility.

(d) Substantial loss of equipment or resources.

(5) **External Noncompliance Findings.** Any findings of noncompliance related to research laboratory security by any VA office, any other Federal department or agency (e.g., Department of Homeland Security), or any other entity. The Facility Director's report to ORO must include a copy of the entity's official findings.

c**. Reports to ORO Central Office.** As soon as possible but no later than 5 business days after being informed of any change in an MOU with an affiliate institution or other entity regarding research laboratory security arrangements, the Facility Director must report the change to ORO Central Office, with a copy to the appropriate ORO RO (see App. A, Table 2).

10. REQUIREMENTS RELATED TO RESEARCH INFORMATION PROTECTION

a. **Reports Within the VA Facility.** The VA facility must establish written SOPs to ensure compliance with the reporting requirements of paragraphs 10a(1) through 10c.

(1) Investigators, RCOs, and other members of the VA research community must report the research events listed in subparagraphs 10b and 10c to the ACOS for R as soon as possible, but no later than 5 business days after becoming aware of them. Where applicable, simultaneous reports must be made to the facility Information Security Officer (ISO), Privacy Officer (PO), and/or relevant research oversight committee(s).

(2) The ACOS for R must report the research events listed in subparagraphs 10b and 10c to the Facility Director and the R&D Committee as soon as possible, but no later than 5 business days after becoming aware of them.

(3) An RCO identifying serious or continuing noncompliance, during a regulatory audit, must report the noncompliance to the Facility Director, the ACOS for R, and the R&D Committee as soon as possible, but no later than 5 business days after becoming aware of them. Where applicable, simultaneous reports must be made to the facility ISO, PO, and/or relevant research oversight committee.

b. **Reports to ORO ROs.** The Facility Director must report the following research events to the appropriate ORO RO as soon as possible, but no later than 5 business days after being informed of them (see App. A, Table 1).

(1) **Serious or Continuing Noncompliance.** Any serious or continuing research-related noncompliance with VA or other Federal requirements pertaining to information security or privacy (e.g., 45 CFR 160 and 164, VA Directive 6502, VA Handbook 6500, VHA Handbook 1605.1).

(2) **Unauthorized Activities.** Any unauthorized, research-related access, use, disclosure, transmission, removal, theft, or loss of VA sensitive information, including, but not limited to: protected health information, individually-identifiable private information (as defined in 38 CFR 16.102(f)(2)), confidential information, and Privacy Act-protected information.

(3) **Other Incidents.** Any research-related incidents reportable to the Office of Information and Technology (OI&T) Network and Security Operations Center (NSOC). ***NOTE:*** *Research personnel must adhere to all VA OI&T NSOC requirements, including those under which certain incidents be reported immediately. Research personnel must simultaneously provide such reports to the ACOS for R.*

(4) **External Noncompliance Findings.** Any findings of noncompliance related to research information security or privacy by any VA office, any other Federal department or agency, or any other entity. The Facility Director's report to ORO must include a copy of the entity's official findings.

c. **Reports to ORO Central Office.** As soon as possible, but no later than 5 business days after being informed of any substantive change in an MOU or System Interconnection Agreement (SIA) with an affiliate institution or other entity related to research information security or research privacy arrangements, the Facility Director must report the change to ORO Central Office, with a copy to the appropriate ORO RO (see App. A, Table 2).

11. REQUIREMENTS RELATED TO RESEARCH MISCONDUCT

a. **Procedures.** The full procedures for handling research misconduct allegations are found in VHA Handbook 1058.2 (see App. A, Table 2).

b. **Notification Requirements.** ORO Central Office must be notified as soon as possible (preferably by telephone or email) of any allegation of research misconduct. Subsequent written notification must be provided as specified by ORO Central Office.

12. REFERENCES

a. Biosafety in Microbiological and Biomedical Laboratories (5th Edition). Centers for Disease Control and Prevention and National Institutes of Health.

b. Guide for the Care and Use of Laboratory Animals. National Research Counsel, 1996.

c. Public Health Service Policy on Humane Care and Use of Laboratory Animals. National Institutes of Health.

d. Title 5 CFR Part 334, Temporary Assignments Under the Intergovernmental Personnel Act.

e. Title 7 CFR Part 331, Possession, Use, and Transfer of Select Agents and Toxins.

f. Title 9 CFR Parts 1, 2, 3, and 4. USDA Animal Welfare Act Regulations and Standards.

g. Title 9 CFR Part 121, Possession, Use, and Transfer of Select Agents and Toxins.

h. Title 21 CFR Part 50, Protection of Human Subjects.

i. Title 21 CFR Part 56, Institutional Review Boards.

j. Title 21 CFR Part 312, Investigational New Drug Application.

k. Title 21 CFR Part 812, Investigational Device Exemptions.

l. Title 29 CFR Part 1910, Occupational Safety and Health Standards.

m. Title 29 CFR Part 1960, Federal Employee Occupational Safety and Health Standards.

n. Title 38 CFR Part 16, Protection of Human Subjects.

o. Title 42 CFR Part 73, Select Agents and Toxins.

p. Title 45 CFR Part 160, Administrative Data Standards and Related Requirements: General Administrative Requirements.

q. Title 45 CFR Part 164, Administrative Data Standards and Related Requirements: Security and Privacy.

r. VA Directive 6502, VA Enterprise Privacy Program.

s. VA Handbook 6500, Information Security Program.

t. VHA Directive 1058, Responsibilities of the Office of Research Oversight.

u. VHA Handbook 1050.01, National Patient Safety Improvement Handbook.

v. VHA Handbook 1058.2, Research Misconduct.

w. VHA Handbook 1058.03, Assurance of Protection for Human Subjects in Research.

x. VHA Handbook 1058.04, Debarments and Suspensions based on Research Impropriety in VA Research.

y. VHA Handbook 1200.1, Research and Development Committee Handbook.

z. VHA Handbook 1200.05, Requirements for the Protection of Human Subjects in Research.

aa. VHA Handbook 1200.06, Control of Hazardous Agents in VA Research Laboratories.

bb. VHA Handbook 1200.7, Use of Animals in Research.

cc. VHA Handbook 1200.8, Safety of Personnel Engaged in Research.

dd. VHA Handbook 1605.1, Privacy and Release of Information.

SUMMARY OF REQUIREMENTS FOR REPORTING RESEARCH EVENTS TO THE OFFICE OF RESEARCH OVERSIGHT (ORO)

Table 1. Reports to ORO Regional Offices with a Copy to the Veterans Integrated Service Network (VISN)*

Human	Animal	Safety	Laboratory Security	Information Protection
1. Problems involving risks to subjects or others that are unanticipated and serious and related, or possibly related, to the research, including work-related injuries; interruptions in research activities due to concerns about the safety, rights, or welfare of subjects, staff, or others; and data Monitoring Committee reports or sponsor analysis describing a safety problem. 2. Local adverse events that are unanticipated and serious and related, or possibly related, to the research. 3. Serious or continuing noncompliance as determined by the Institutional Review Board (IRB) or identified by a Research Compliance Officer (RCO) audit, including findings of external entities. 4. Suspensions or terminations of IRB approval related to concerns about the safety, rights, or welfare of subjects, staff, or others, including suspensions by the IRB of new enrollments or other research activities.	1. Any unanticipated incident that seriously affects the health or safety of laboratory animals. 2. Any unanticipated loss of animal life, including loss due to physical plant or engineering problems. 3. Work-related injury to personnel, or research-related injury to any person, requiring more than minor medical intervention or leading to serious complications or death. 4. Any serious or continuing noncompliance with, or deviations from, VA or other Federal requirements. 5. Suspensions or terminations of ongoing animal research activities related to concerns regarding the safety or welfare of animals or the safety, rights, or welfare of staff or others. 6. Findings of noncompliance by external entities.	1. Work-related injury to personnel, or research-related injury to any person, requiring more than minor medical intervention or leading to serious complications or death. 2. Work-related exposure of research personnel to hazardous materials at greater than routine levels or requiring more than minor medical intervention or leading to serious complications or death. 3. Any serious or continuing noncompliance with VA or other Federal requirements. 4. Suspensions or terminations of ongoing research activities related to concerns regarding the safety, rights, or welfare of research staff or others. 5. Findings of noncompliance by external entities.	1. Any injury or harm to a human being or laboratory animal related to a break-in, security breach, or other problem involving a VA research facility. 2. Any serious or continuing noncompliance with VA or other Federal requirements. 3. Any break-in or security breach involving a VA Biosafety Level 3 (BSL-3) research laboratory. 4. Any break-in or security breach involving a VA research facility that results in: a. Loss of any quantity of select agent or toxin. b. Substantial damage to the facility. c. Loss of equipment or resources. 5. Findings of noncompliance by external entities.	1. Any serious or continuing noncompliance with VA or other Federal requirements. 2. Any unauthorized, research-related access, use, disclosure, transmission, removal, theft, or loss of protected health information, individually identifiable private information, confidential information, Privacy Act protected information, or other VA sensitive information. 3. Any research-related incidents reportable to the Office of Information and Technology (OI&T) Network and Security Operations Center (NSOC). 4. Findings of noncompliance by external entities.

***NOTE:** Members of the VA research community, including RCOs, must notify the Associate Chief of Staff for Research and relevant oversight committee as soon as possible but no later than 5 business days after becoming aware of these events. The Facility Director must notify ORO in writing as soon as possible but no later than 5 business days after being informed of these events.*

SUMMARY OF REQUIREMENTS FOR REPORTING RESEARCH EVENTS TO ORO

Table 2. Reports to ORO Central Office (with copy to ORO Regional Office and VISN) *

Human	Animal	Safety	Laboratory Security	Information Protection
1. Any change in the facility's Federalwide Assurance (FWA) or other ORO-approved Assurance, 2. Any change in the facility's designated IRB(s). 3. Any change in an memorandum of Understanding (MOU) related to the designation of IRBs or other human research protection arrangements. 4. Failure of the VA facility to achieve "full accreditation" status from the VA human research accreditation organization, any change in the facility's accreditation status, or any change in the accreditation status of an affiliate involved in the facility's human research protection program.	1. Any change in the facility's Public Health Service (PHS) Animal Welfare Assurance as filed with the Office of Laboratory Animal Welfare (OLAW). 2. Any change in the status of the PHS Animal Welfare Assurance of an affiliate or other entity on which the facility relies. 3. Any change in an MOU related to laboratory animal welfare or animal care and use arrangements 4. Failure of the VA facility to achieve "full accreditation" status from the VA animal research accreditation organization, any change in the facility's accreditation status, or any change in the accreditation status of an affiliate involved in the facility's animal care and use program.	1. Any change in an MOU related to research safety arrangements.	1. Any change in an MOU related to research laboratory security arrangements.	1. Any change in an MOU or System Interconnection Agreement related to research information security arrangements.

***NOTE:** Members of the VA research community, including RCOs, must notify the ACOS for Research and relevant oversight committee as soon as possible, but no later than 5 business days after becoming aware of these events. The Facility Director must notify ORO in writing as soon as possible, but no later than 5 business days after being informed of these events.*

SUMMARY OF REQUIREMENTS FOR REPORTING RESEARCH EVENTS TO THE OFFICE OF RESEARCH OVERSIGHT (ORO)

Table 3. Notification to ORO Central Office – Research Misconduct*

Research Misconduct
1. Notify ORO Central Office as soon as possible (preferably by telephone or email) about any allegation of research misconduct. Subsequent written notification must be provided as specified by ORO Central Office. 2. Notification needs to include whether or not the allegation involves any of the following: a. Harm or threat of harm to research subjects. b. Harm or threat of harm to those involved in an inquiry or investigation. c. Serious violations of animal welfare requirements. d. Research safety or security compromises. e. Risks to public health or safety. f. Loss or destruction of VA funds or property. g. Possible violations of civil or criminal law. 3. Notify ORO Central Office of the following related to any research misconduct proceeding: a. Opening of a research misconduct inquiry. b. Requests for changes or departures from VHA Handbook 1058.2 (ORO approval required). c. Extensions of the inquiry review period (ORO approval required). d. Closure of a research misconduct inquiry without further investigation (include Inquiry Report and the concurrence of Facility Director). e. Opening of a research misconduct investigation. f. Extensions of the investigation review period (ORO approval required). g. Closure of a research misconduct investigation (include Investigation Report and recommendations of Facility Director). h. Decision of the Veterans Integrated Service Network (VISN) Director.

*** *NOTE:*** *Consult ORO's Web site at: www1.va.gov/oro/ , and VHA Handbook 1058.2 for complete reporting requirements and procedures related to allegations of research misconduct.*

ADVERSE EVENTS IN RESEARCH AS UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS

1. Federal Policy. The Federal Policy (Common Rule) for the Protection of Human Subjects and Department of Veterans Affairs (VA) regulations at Title 38 Code of Federal regulations (CFR) 16.103(b)(5) require written procedures for promptly reporting the following to the Institutional Review Board (IRB), institutional officials, and the Department or Agency Head:

a. Unanticipated problems involving risks to subjects or others.

b. Serious or continuing noncompliance with regulatory requirements or IRB requirements or determinations.

c. Suspensions or terminations of IRB approval.

2. Food and Drug Administration (FDA) IRB Regulations. FDA IRB regulations at 21 CFR 56.108(b)(1) contain the identical reporting requirements.

3. FDA Device Regulations. FDA device regulations at 21 CFR 812.150(a)(1) require that the investigator report serious unanticipated adverse device effects to the IRB no later than 10 business days after the investigator first learns of the effect.

4. FDA Drug Regulations. Neither the VA human subject protection regulations (Common Rule) nor the FDA investigational new drug regulations at 21 CFR 312 contain explicit requirements for promptly reporting adverse drug events to the IRB when the adverse drug events do not constitute unanticipated problems involving risks to subjects or others.

5. VHA Policy Requirements. VHA Handbook 1200.5 indicates that individual data and safety monitoring plans for reporting Adverse Events (AEs) to the IRB may vary depending upon the potential risks, complexity, and nature of the study. VHA Handbook 1200.5 requires that the IRB establish written procedures for notifying medical center officials and VA Central Office of any AEs that cause "harm or risk of harm to human subjects or groups."

6. AEs as Unanticipated Problems. Except for serious, unanticipated adverse device effects, Federal regulations require that AEs be reported promptly to the IRB only when they constitute unanticipated problems involving risks to subjects or others.

7. Unanticipated Problems versus AEs. Unanticipated Problems Involving Risks (UPRs) to subjects or others and AEs constitute overlapping, but not identical, concepts (see Figure 1 of App. B).

a. UPRs include both risks to subjects and risks to other individuals (e.g., research personnel, subjects' family members). Risks may reflect any type of potential harm (e.g., physical, psychological, social, economic, and breach of privacy).

b. UPRs include some (but not all) AEs, and AEs include some (but not all) UPRs.

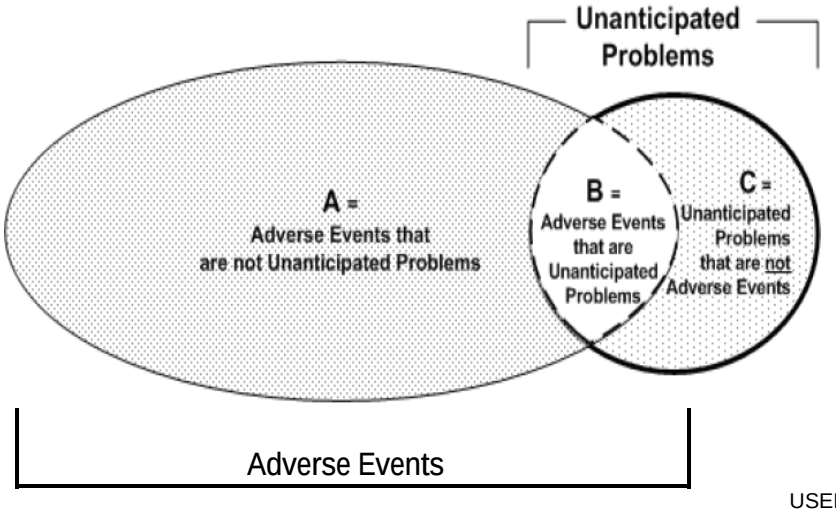

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Figure 1*. *UPRs and AEs constitute overlapping, but not identical, concepts. *UPRs include some (but not all) AEs, and AEs include some (but not all) UPRs.*

8. AEs That Are Not UPRs. Examples include the following situations:

a. A subject experiences soreness and redness at the investigational drug injection site that are consistent in nature, severity, and frequency of occurrence with anticipated side effects described in the IRB-approved protocol and consent document.

b. A subject experiences anxiety and stress (in response to interview questions about a traumatic event) that are consistent in nature, severity, and frequency of occurrence with anticipated reactions described in the IRB-approved protocol and consent document.

9. AEs That Are UPRs. Examples include the following situations:

a. A subject experiences soreness and redness at the investigational drug injection site that are more severe than anticipated side effects described in the protocol and consent document.

b. More subjects than anticipated in the protocol and disclosed in the consent document experience anxiety and stress in response to interview questions about a traumatic event.

c. Two hours after receiving an investigational drug, a subject experiences intense headache and vomiting that last about an hour and then resolve. Neither was described in the protocol or consent document as a possible side effect of the research.

10. UPRs That Are Not AEs. Examples include the following situations:

a. A subject mistakenly receives twice the dose of an investigational drug than was stipulated in the protocol, but suffers no side effects and no indication of harm.

b. A subject receives one dose of active drug instead of placebo but suffers no side effects and no indication of harm.

c. A laptop containing identifiable private information is stolen from a research lab but is recovered from a campus dumpster several hours later. Data files remain intact.

d. A research assistant suffers a severe burn due to malfunctioning research equipment.

e. During an interview about children's play, a parent-subject confesses a continuing problem with child abuse. Materials approved by the IRB did not address how such situations would be handled.

f. The investigator receives a Data Monitoring Committee (DMC) report indicating that researchers should look out for a particular side effect that may be occurring more frequently than anticipated.

g. The sponsor suspends new enrollments in a trial due to suspected manufacturing problems.

h. New studies in the published literature suggest that the drug being used in a research study may be associated with a previously unknown risk of stroke.

11. Requirements for Reporting to the IRB. UPRs must be reported to the IRB in accordance with VA's codification of the Common Rule at 38 CFR 16.103(b)(5) and subparagraph 6a(3) of the Handbook.

a. Local SAEs and problems involving risks to subjects, or others, must be reported to the IRB and the Associate Chief of Staff for Research within 5 business days.

b. Figure 2 of Appendix B provides a "yes/no" decision chart to identify situations involving problems and SAEs that must be reported to the IRB.

12. Standard Operating Procedures (SOPs) for Reporting to the IRB. SOPs, providing detailed instructions on reporting research events to the IRB, must be developed at VA research facilities.

a. VA investigators must consistently and reliably satisfy the requirements for reporting to the IRB.

b. VA facilities may use a variety of strategies (e.g., mandatory training, monitoring) to ensure full compliance with the requirements for reporting UPRs to the IRB.

13. SOPs for Reporting to ORO

a. VA Facility Directors are responsible for ensuring:

(1) Detailed instructions on reporting UPRs and AEs to ORO are developed at each research facility.

(2) Problems in human research involving risks to subjects, or others, are reported to the appropriate ORO RO when they:

(a) Involve risks to subjects or others; and

(b) Are determined, according to subparagraph 6a(3) of the Handbook, to be serious and unanticipated and related, or possibly related, to the research.

b. Figure 2 of Appendix B provides a "yes/no" decision chart to identify situations involving serious problems and SAEs that must be reported to the appropriate ORO RO.

c. Figure 3 of Appendix B illustrates the subset of UPRs and AEs that must be reported to the appropriate ORO Regional Office (RO).

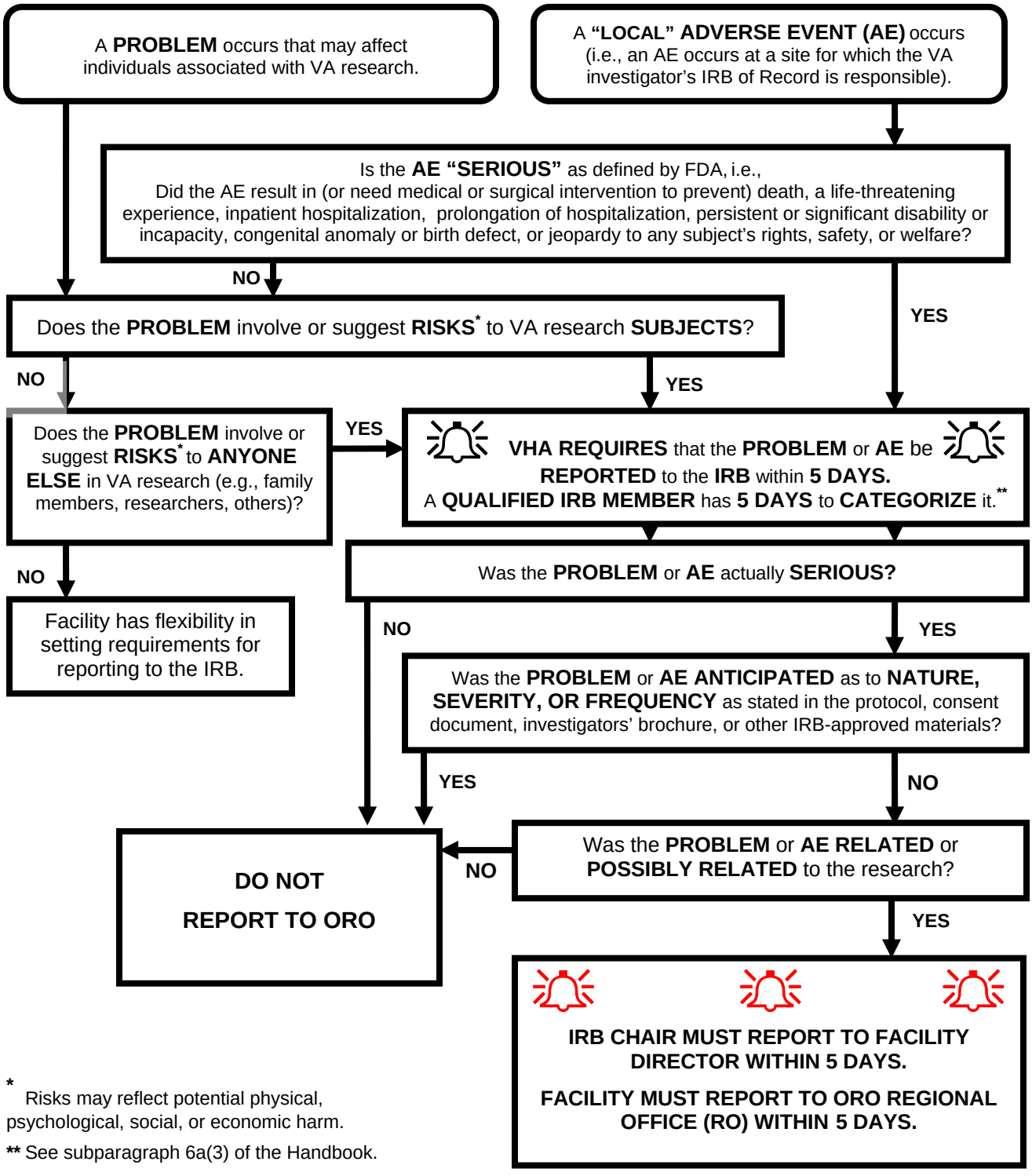

Figure 2. Decision chart for reporting UPRs and AEs to the IRB and ORO. *Reports should be sent to the appropriate ORO Regional Office.*

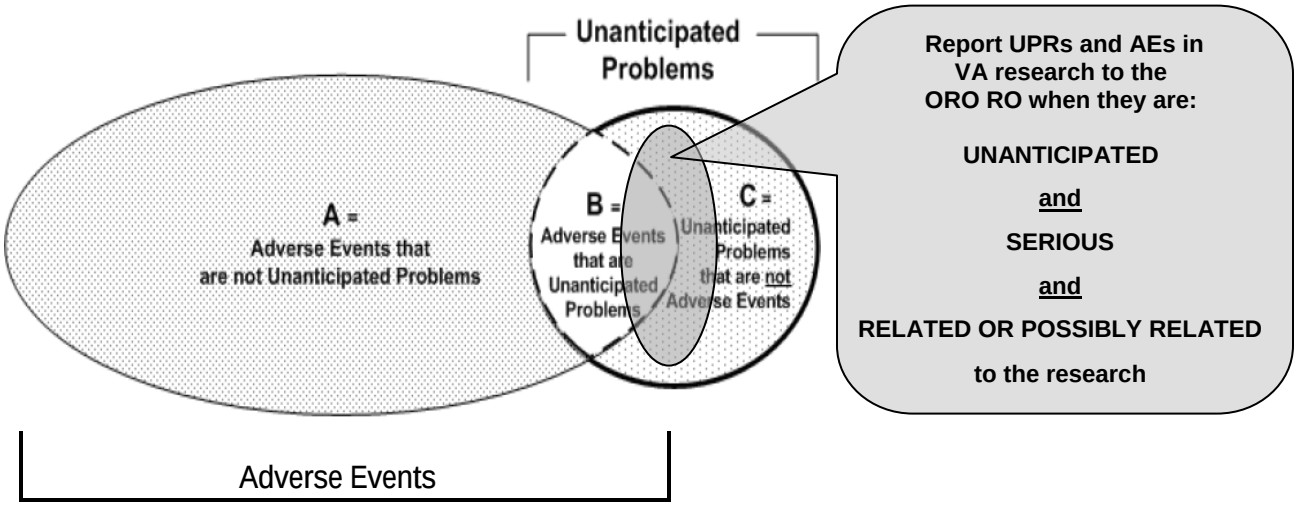

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Figure 3*. *UPRs, including certain AEs, must be reported to ORO. *Reports need to be sent to the ORO RO responsible for oversight of the facility when the UPRs or AEs:*
(a) Occur at a VA facility or in research conducted by individuals acting as VA employees, and
(b) Are found by the IRB to be unanticipated and serious and related to the research.